WHAT IS CLAIMED IS:

1. A method of labeling a molecule exposed on a luminal surface of a perfusible space *in situ* or *in vivo* comprising the following steps:

(a) providing a cell membrane impermeable reagent comprising three domains

(i) a first domain comprising a chemical moiety capable of covalently and non-specifically binding to a molecule exposed on the luminal surface of a cell lining a perfusible space *in situ* or *in vivo*,

(ii) a second domain comprising a labeling domain, and

(iii) a third domain situated between the first and second domains linking the first domain to the second domain by a cleavable chemical moiety, wherein the cleavable chemical moiety will not cleave under *in vivo* conditions; and

(b) administering the membrane impermeable reagent into the perfusible space in an intact organ or an intact animal to react the cell membrane impermeable reagent with the molecule expressed on the luminal surface of the cell lining the perfusible space to label a lumen-exposed molecule.

2. The method of claim 1, wherein the lumen-exposed molecule is an organ-specific or a tissue-specific molecule.

3. The method of claim 1, wherein the perfusible space is a lumen of a vascular vessel and the cell lining the space is an endothelial cell.

4. The method of claim 3, wherein the vascular vessel is an artery, an arteriole, a vein, or a capillary.

5. The method of claim 1, wherein the perfusible space is a lumen of a cerebral spinal fluid (CSF) space.

6. The method of claim 1, wherein the perfusible space is a lumen of a lymphatic vessel and the cell lining the space is an endothelial cell.

7. The method of claim 1, wherein the perfusible space is a lumen of an endocrine or exocrine duct or pore.

8. The method of claim 1, wherein the cell lining the perfusible space is an epithelial cell.

9. The method of claim 1, wherein the organ is, or the tissue is derived from, a heart, a lung, a brain, a liver, a kidney, an endocrine gland, skin, a reproductive organ, a digestive tract organ, or an eye.

Sub F1

10. The method of claim 1, wherein the labeling domain of the reagent comprises biotin.

11. The method of claim 1, wherein the labeling domain of the reagent is a polypeptide, a nucleic acid, a peptide nucleic acid (PNA), a fluorescent molecule, a colorimetric agent, a radionuclide, a naturally occurring or a synthetic organic molecule or a chelate.

12. The method of claim 11, wherein the polypeptide comprises a polyhistidine.

13. The method of claim 1, wherein the cleavable chemical moiety comprises a disulfide group.

14. The method of claim 1, wherein the cleavable chemical moiety comprises a periodate-cleavable glycol, a dithionite-cleavable diazobond, a hydroxylamine-cleavable ester or a base-labile sulfone.

15. The method of claim 1, wherein the cell membrane impermeable reagent further comprises a fourth domain comprising a binding domain.

16. The method of claim 1, wherein administering the cell membrane impermeable reagent into the perfusible space of the intact organ or tissue or the intact animal comprises administration of a buffered, aqueous solution comprising the cell membrane impermeable reagent.

17. The method of claim 1, wherein the molecule exposed on the luminal surface of the perfusible space and labeled by the cell membrane impermeable reagent is a polypeptide.

18. The method of claim 1, wherein the molecule exposed on the luminal surface of the perfusible space and labeled by the cell membrane impermeable reagent is a lipid or a carbohydrate.

19. A method of isolating a molecule that is exposed on a luminal surface of a perfusible space comprising the following steps:

(a) providing a cell membrane impermeable reagent comprising three domains

(i) a first domain comprising a chemical moiety capable of covalently and non-specifically binding to a molecule expressed on the luminal surface of a cell lining a perfusible space *in situ* or *in vivo*,

(ii) a second domain comprising a binding domain;

(b) administering the cell membrane impermeable reagent into the perfusible space in an intact organ or an intact animal to react the cell membrane impermeable reagent with a molecule expressed on the luminal surface of the cell lining the perfusible space; and

(c) isolating the reagent-reacted molecule.

20. The method of claim 19, wherein the lumen-exposed molecule is an organ-specific or a tissue-specific molecule.

21. The method of claim 20, further comprising the step of comparing the reagent-reacted molecules from different organs or tissues to identify an organ-specific or tissue-

specific molecule, wherein the organ-specific or tissue-specific molecule is exposed on the luminal surface of the perfusible space of only one of the compared organs or tissues.

22. The method of claim 19, wherein the perfusible space is a lumen of a vascular vessel and the cell lining the space is an endothelial cell.

23. The method of claim 22, wherein the vascular vessel is an artery, an arteriole, a vein, or a capillary.

24. The method of claim 19, wherein the perfusible space is a lumen of a cerebral spinal fluid (CSF) space.

25. The method of claim 19, wherein the perfusible space is a lumen of a lymphatic vessel and the cell lining the space is an endothelial cell.

26. The method of claim 19, wherein the perfusible space is a lumen of an endocrine or exocrine duct or pore.

27. The method of claim 19, wherein the cell lining the perfusible space is an epithelial cell.

28. The method of claim 19, wherein the organ is, or the tissue is derived from, a heart, a lung, a brain, a liver, a kidney, an endocrine gland, skin, a reproductive organ, a digestive tract organ, or an eye.

29. The method of claim 19, wherein the binding domain of the reagent comprises biotin.

30. The method of claim 19, wherein the binding domain of the reagent comprises a polypeptide, a nucleic acid, a peptide nucleic acid, a naturally occurring or a synthetic organic molecule or a chelate.

31. The method of claim 30, wherein the polypeptide comprises a polyhistidine.

32. The method of claim 19, wherein the cleavable chemical moiety comprises a disulfide group.

33. The method of claim 19, wherein the cleavable chemical moiety comprises a periodate-cleavable glycol, a dithionite-cleavable diazobond, a hydroxylamine-cleavable ester or a base-labile sulfone.

34. The method of claim 19, wherein the cell membrane impermeable reagent further comprises a fourth domain comprising a molecule that facilitates detection of the reagent.

35. The method of claim 34, wherein the fourth domain molecule that facilitates detection comprises a fluorescent molecule, a colorimetric agent or a radionuclide.

36. The method of claim 19, wherein administering the cell membrane impermeable reagent into the perfusible space of the intact organ or tissue or the intact animal comprises administration of a buffered, aqueous solution comprising the cell membrane impermeable reagent.

37. The method of claim 19, wherein the molecule exposed on the luminal surface of the perfusible space and isolated by the cell membrane impermeable reagent is a polypeptide.

38. The method of claim 19, wherein the molecule exposed on the luminal surface of the perfusible space and isolated by the cell membrane impermeable reagent is a lipid or a carbohydrate.

39. The method of claim 19, wherein two separate cell membrane impermeable reagents are co-administered.

40. The method of claim 19, wherein the reagent-reacted molecule is isolated by

(a) contacting a cell or a membrane isolate or a cell or a tissue homogenate or an extract derived from the reagent-reacted organ or animal with a ligand having affinity for the binding domain of the cell membrane impermeable reagent; and

(b) removing a non-bound molecule from the ligand-bound molecules.

41. The method of claim 40, wherein the ligand is immobilized.

42. The method of claim 41, wherein the ligand is immobilized on a bead.

43. The method of claim 40, wherein the binding domain ligand is an avidin or a strepavidin molecule.

44. The method of claim 40, wherein the reagent-reacted molecule is further isolated by removing substantially all of the non-bound molecule from the ligand-bound molecules.

45. The method of claim 40, wherein the non-bound molecule is removed by washing.

46. The method of claim 40, wherein the reagent-reacted molecule is further isolated by cleavage of the cleavable chemical moiety of the cell membrane impermeable reagent after removing a non-bound molecule.

47. The method of claim 46, wherein the conditions for cleaving the cleavable chemical moiety do not denature the reacted and isolated organ- or tissue- specific molecule.

48. The method of claim 46, wherein the conditions for cleaving the cleavable chemical moiety do not dissociate the binding domain from the ligand.

49. The method of claim 46, wherein the reagent-reacted molecule is further isolated by elution from the binding domain and the ligand.

50. The method of claim 46, wherein the conditions for cleaving the chemical moiety comprise mild reducing, non-denaturing conditions.

51. A method of isolating an organ-specific or tissue-specific molecule that is exposed on a luminal surface of an arteriole, a capillary or a vein comprising the following steps:

(a) providing a cell membrane impermeable reagent comprising three domains

(i) a first domain comprising an active moiety capable of covalently and non-specifically binding to a molecule expressed on the luminal surface of a cell lining a perfusible space *in situ* or *in vivo*,

(ii) a second domain comprising a biotin binding domain, and

(iii) a third domain comprising a disulfide moiety situated between the first and second domains linking the first domain to the second domain; and

(b) administering the cell membrane impermeable reagent into a lumen of an artery, a arteriole, a capillary or a vein in an intact organ or an intact animal to react the cell membrane impermeable reagent with a molecule expressed on the luminal surface; and isolating the reagent-reacted molecule by contacting with an immobilized avidin or strepavidin molecule and removing substantially all of the non-immobilized molecules.

52. A kit comprising

a cell membrane impermeable reagent comprising three domains: (i) a first domain comprising an active moiety capable of covalently and non-specifically binding to a molecule expressed on the luminal surface of a cell lining a perfusible space *in situ* or *in vivo*, (ii) a second domain comprising a binding domain, and, (iii) a third domain comprising a disulfide moiety situated between the first and second domains linking the first domain to the second domain; and

printed matter instructing use of the cell membrane impermeable reagent for administration into a lumen of an intact organ or an intact animal to react the cell membrane

impermeable reagent with a molecule expressed on the luminal surface to isolate the reagent-reacted molecule.

53. The kit of claim 52, wherein the binding domain of the cell membrane impermeable reagent is biotin and the printed matter instructs isolation of the reagent-reacted molecule by contact with an immobilized avidin or strepavidin molecule and removing substantially all of the non-immobilized molecules.

54. The kit of claim 52, wherein the printed matter instructs administration into a lumen of an artery, a arteriole, a capillary or a vein.